Journal of Physiology (2002), **543.1**, *pp.* 373–378
DOI: 10.1113/jphysiol.2002.019380

www.jphysiol.org

Interleukin-6 production in human subcutaneous abdominal adipose tissue: the effect of exercise

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The interleukin-6 (IL-6) output from subcutaneous, abdominal adipose tissue was studied in nine healthy subjects before, during and for 3 h after 1 h two-legged bicycle exercise at 60 % maximal oxygen consumption. Seven subjects were studied in control experiments without exercise. The adipose tissue IL-6 output was measured by direct Fick technique. An artery and a subcutaneous vein on the anterior abdominal wall were catheterized. Adipose tissue blood flow was measured using the ^{133}Xe-washout method. In both studies there was a significant IL-6 output in the basal state and no significant change was observed during exercise. Post-exercise the IL-6 output began to increase after 30 min. Three hours post-exercise it was 58.6 ± 22.2 pg (100 g)$^{-1}$ min^{-1}. In the control experiments the IL-6 output also increased, but it only reached a level of 3.5 ± 0.8 pg (100 g)$^{-1}$ min^{-1}. The temporal profile of the post-exercise change in the IL-6 output closely resembles the changes in the outputs of glycerol and fatty acids, which we have described previously in the same adipose tissue depot. The difference is that it begins to increase ~30 min before the glycerol and fatty acid outputs begin to increase. Thus, we suggest that the enhanced IL-6 production post-exercise in abdominal, subcutaneous adipose tissue may act locally via autocrine/paracrine mechanisms influencing lipolysis and fatty acid mobilization rate from this lipid depot.

(Resubmitted 21 February 2002; accepted after revision 20 May 2002)
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The establishment of adipose tissue as not just an energy depot but also as an endocrine organ has revealed the possibility that the hormones released from the adipose tissue may mediate the complications associated with obesity (Mohamed-Ali *et al.* 1998; Ahima & Flier, 2000; Ailhaud, 2000; Fruhbeck *et al.* 2001). The cytokine interleukin 6 (IL-6) is one of the proteins secreted by the subcutaneous adipose tissue (Mohamed-Ali *et al.* 1997, 1999; Orban *et al.* 1999). The IL-6 level in plasma is elevated in obesity (Yudkin *et al.* 1999; Bastard *et al.* 2000; Kern *et al.* 2001; Vozarova *et al.* 2001) and it correlates with fat mass (Vozarova *et al.* 2001) and body mass index (BMI) (Yudkin *et al.* 1999; Bastard *et al.* 2000; Kern *et al.* 2001; Vozarova *et al.* 2001). This might be due to increased fat mass secreting more IL-6. IL-6 also correlates with fasting insulin levels (Bastard *et al.* 2000; Fernandez-Real *et al.* 2001; Vozarova *et al.* 2001) and is associated with insulin sensitivity (Yudkin *et al.* 1999; Kern *et al.* 2001; Fernandez-Real *et al.* 2001; Vozarova *et al.* 2001). A higher level of IL-6 in plasma is seen in type 2 diabetes mellitus patients (Bastard *et al.* 2000; Pickup *et al.* 2000). Recently, it has been shown that IL-6-deficient mice develop obesity (Wallenius *et al.* 2002). Thus, there is substantial evidence showing that IL-6 may be associated with the metabolic activity in adipose tissue. IL-6 has been suggested to have paracrine effects in adipose tissue. For example, IL-6 decreases lipoprotein lipase (LPL) activity (Greenberg *et al.* 1992), and in infusion studies IL-6 seems to induce lipid mobilization in rats, and in cancer patients, however, at IL-6 concentrations also giving rise to increased adrenaline concentrations (Nonogaki *et al.* 1995; Stouthard *et al.* 1995). Exercise is a powerful stimulator of lipolysis in adipose tissue, the mediating mechanisms being increased sympatico-adrenergic activity in combination with decreased insulin concentration (Bülow, 1993). We have recently described a post-exercise lipolytic response in abdominal, subcutaneous adipose tissue (Mulla *et al.* 2000). Immediately post-exercise the glycerol and fatty acid mobilization rates decreased to the pre-exercise level. About 1 h post-exercise they began to increase again and reached values at the exercise level after 3 h. The mechanism eliciting this post-exercise lipolytic response has not been identified, but it is unlikely that it is the same as those eliciting the increased lipolysis during exercise. One possibility is that substances with lipolytic effects are produced *in situ* in adipose tissue. A likely candidate is IL-6, since IL-6 is produced in adipose tissue and has been proposed to have lipolytic effects. The aim of the present study was, therefore, to measure the IL-6 secretion from abdominal, subcutaneous adipose tissue before, during and for 3 h into the recovery period following moderate exercise, and in control experiments of similar duration without exercise.

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METHODS

Subjects

Nine subjects (8 males) participated in the exercise experiment. Mean (± S.E.M.) age, height and weight were 23.6 ± 0.4 years, 183 ± 2 cm and 78 ± 2 kg, respectively. Total body fat mass was 14.5 ± 3.0 kg as determined by DEXA scanning (Lunar DPX-IQ, software version 4.6c, Madison, WI, USA). Seven subjects (5 males, of whom 2 also participated in the exercise experiment) were studied in the control experiment. Mean age, height and weight were 24.0 ± 0.3 years, 179 ± 2 cm and 73 ± 3 kg. Total body fat mass was 13.9 ± 1.5 kg. The female subjects were studied within the first 14 days of the menstrual cycle.

Subjects were given a written and oral description of the study according to the Declaration of Helsinki, and their written consent was obtained. The study was approved by The Ethical Committee for Medical Research of Copenhagen (project nos KF 01-201/98 and KF 02-010/00).

Experimental protocols

Prior to the experiments the subjects performed a test to determine their maximal oxygen uptake ($\dot{V}_{O_2,max}$). They exercised in a semirecumbent position on an electrically braked cycle ergometer (ergometrics er900L, ergoline, Bitz, Germany). The initial workload was 50 W and was increased by 50 W every 2 min until exhaustion. Oxygen uptake and carbon dioxide output were measured continuously using an Oxycon Champion System (Jaeger, Wuerzburg, Germany) using a facemask and the breath-by-breath technique.

Exercise experiment

The subjects came to the laboratory at 08.00 h after an overnight fast. In the days prior to the experiment the subjects ate their usual diet and performed their usual physical activities. However, for the last 24 h before the experiment they refrained from vigorous physical activity.

The exercise experiment consisted of a pre-exercise rest period, an exercise period and a post-exercise period. The pre-exercise rest period started when the subject was in a steady-state situation with respect to whole-body oxygen consumption and adipose tissue blood flow. The pre-exercise rest period was of 30 min duration, and was followed by an exercise period of 1 h where the subjects exercised at 60 % $\dot{V}_{O_2,max}$. The exercise was performed in a semirecumbent position. After the exercise period the subjects were studied during rest for another 3 h. The pre- and post-exercise periods were performed in a recumbent position.

Control experiment

The subjects came to the laboratory at 08.00 h after an overnight fast and followed the same procedures prior to the experiment as the subjects participating in the exercise experiment. The control experiment consisted of 6.5 h rest, where the same parameters as in the exercise experiment were studied.

Catheterization

In each subject a catheter (Artflon, Ohmeda, Swindon, UK) was inserted into a radial artery, after injection of 0.5 ml of 1 % lidocaine (lignocaine). A subcutaneous, abdominal vein was catheterized during ultrasound/colour Doppler imaging of the vein as described previously (Simonsen *et al.* 1994). This technique enables catheterization of a vein deep in the subcutaneous adipose tissue that mainly drains adipose tissue. A 22 G 10 cm polyurethane catheter (Ohmeda) was inserted using the Seldinger technique. The catheter was kept patent throughout the experiment by continuous infusion of isotonic sodium chloride at a rate of 40 ml h^{-1}.

Blood flow measurements

Blood flow through the abdominal subcutaneous adipose tissue was measured using the ^{133}Xe-washout technique as previously described (Bülow, 1983). About 1 MBq ^{133}Xe dissolved in 0.1 ml isotonic sodium chloride was injected into the subcutaneous abdominal adipose tissue contralateral to the catheter. The washout of ^{133}Xe was measured by a scintillation counter system strapped to the skin surface above the region with the ^{133}Xe depot (Oakfield Instruments, Oxford, UK). The adipose tissue blood flow was calculated from the wash-out rate as previously described assuming a tissue/blood partition coefficient value of 8 ml ml^{-1} (Bülow *et al.* 1987).

Blood sampling

Blood samples were drawn simultaneously from the catheters. In the exercise experiment three samples were taken in the pre-exercise period and the average of these three samples was used as the pre-exercise resting concentration. One blood sample was drawn after 60 min of exercise, just before termination of exercise. In the post-exercise period blood was drawn every 30 min for 3 h. In the control experiment blood samples were drawn every 60 min. The blood was collected in vials at 4 °C, and the plasma was separated by centrifugation at 4 °C. The samples were stored at −20 °C until analysis.

Blood analyses

Plasma IL-6 concentration was measured by highly sensitive enzyme immunoassays (Quantikine HS, R&D systems, Minneapolis, USA). The assay has a limit of detection of 0.094 ng l^{-1} and an intra-assay coefficient of variation of 5.9 %.

Whole-body measurements

Whole-body oxygen consumption and respiratory exchange ratio were measured using a facemask and the breath-by-breath technique during the pre-exercise and the exercise periods. These measurements were carried out with the same system as used for the determination of maximal oxygen uptake. During the experiment the heart rate and intra-arterial blood pressure were monitored by an Athena (S&W, Copenhagen, Denmark) interfaced to the Oxycon Champion system.

Calculations

The adipose tissue output of IL-6 was determined by multiplication of the veno-arterial (v−a) IL-6 concentration difference and the plasma flow.

Statistics

All data are presented as means ± S.E.M.. Trends over time were analysed with two-way ANOVA using Minitab release 10 (Minitab Inc., PA, USA). $P < 0.05$ was considered significant.

RESULTS

In the exercise group peak oxygen uptake was 3802 ± 209 ml min^{-1}. The mean oxygen uptake rate and the respiratory exchange ratio during exercise were 2171 ± 173 ml min^{-1} and 0.84 ± 0.03, respectively. In the control group peak oxygen uptake was 3615 ± 254 ml min^{-1}.

Figure 1*A* shows the IL-6 concentration in arterial blood in the exercise and control studies. In the exercise study the IL-6 concentration increased significantly with time

($P = 0.002$) the increase being most pronounced during exercise. The concentration remained constant in the control study ($P = 0.619$). Figure 1*B* shows the adipose tissue veno-arterial IL-6 concentration difference. In the exercise study this difference increased to ~20 ng l^{-1} in the post-exercise resting period. In the control study the v–a concentration difference also increased with time ($P = 0.039$), but only to ~4 ng l^{-1}. Figure 1*C* shows the adipose tissue IL-6 secretion rates. In both studies there was a net secretion of IL-6 in the baseline period. In the exercise study it increased to ~60 pg $(100\ g)^{-1}\ min^{-1}$. In the control study it increased to ~3.5 pg $(100\ g)^{-1}\ min^{-1}$ ($P = 0.039$).

Figure 2 shows the adipose tissue blood flow in the two studies. In the exercise study the blood flow increased during exercise. Immediately post-exercise it decreased to the pre-exercise level. About 1 h post-exercise it began to increase again and was still increasing at the end of the experiment. In the control experiment the blood flow remained virtually constant with time ($P = 0.779$).

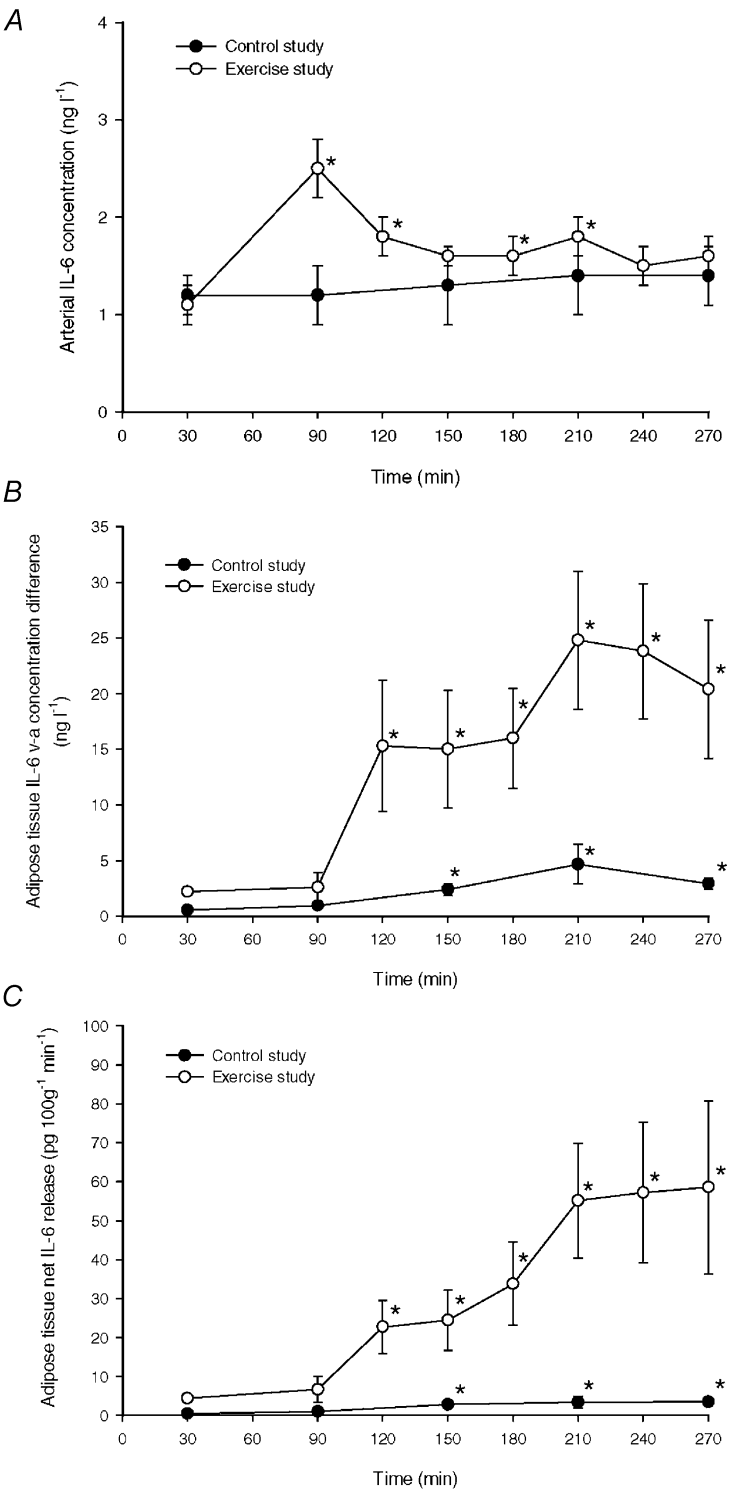

Figure 1

Data are presented as means ± S.E.M.
* Significant difference ($P < 0.05$) from the baseline (30 min) value. ○, the study including a 60 min exercise period. ●, the control study without exercise. *A*, arterial plasma IL-6 concentrations. *B*, adipose venous–arterial (v–a) concentration differences calculated as venous − arterial plasma IL-6 concentrations. *C*, net release of IL-6 calculated as the product of the (v–a) concentration difference and adipose tissue plasma flow.

DISCUSSION

The present experiments confirm the finding in Mohamed-Ali *et al.* (1997, 1999) that the subcutaneous, abdominal adipose tissue is a net exporter of IL-6 in the post-absorptive, fasting state during rest in man. The main new finding is that this output begins to increase ~30 min post-exercise, and increases steadily to the end of the study. Three hours post-exercise the net IL-6 output was ~15-fold higher than the output found in the control experiments. The increased output is therefore a consequence of the exercise. In the control experiments there was a slight but significant increase in the IL-6 output with time. Whether this increase is due to the extended fasting, or whether it is due to a local inflammatory reaction in the vein induced by the catheter cannot be answered from the present experiments. In addition, there may be diurnal variations in the IL-6 secretion, as Mohamed-Ali *et al.* (1997) have found higher secretion rates early in the evening compared with late morning independent of whether the subjects were in the absorptive or post-absorptive state.

We have previously described that post-exercise there is an increase in the glycerol and fatty acid mobilization from subcutaneous, abdominal adipose tissue (Mulla *et al.* 2000) beginning ~60 min after exercise. This was mainly brought about by an increase in the adipose tissue blood flow. In contrast, the increase in the IL-6 output is mainly brought about by an increase in the adipose vein concentration. This implies that the tissue IL-6 concentration must also have increased. The mechanisms eliciting these post-exercise responses are not known. However, it should be noted that the adipose tissue IL-6 output had the same temporal profile as the glycerol and fatty acid outputs, but it began to increase ~30 min earlier. Whether this is only a temporal or a causal relationship remains to be shown.

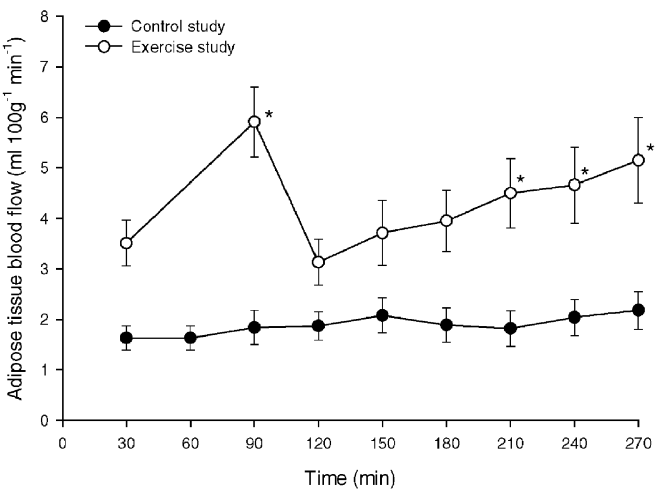

Figure 2

Subcutaneous, abdominal adipose tissue blood flow in the experiment with a 60 min exercise period (○), and in the control experiment without exercise (●).

Assuming that the secretion rate measured in the present experiments post-exercise is representative of the 'average' adipose tissue secretion rate, the total amount of IL-6 being secreted 2 and 3 h post-exercise is ~6–7 ng min^{-1}. This is very similar to the secretion rate found by Steensberg *et al.* (2000) from a lower extremity after 4 h of one-legged knee extensor exercise. In that study the arterial IL-6 concentration was ~4-fold higher than the concentration found in the present experiments. There are two possible explanations for this discrepancy. First, the anterior, abdominal subcutaneous adipose tissue IL-6 secretion may not be representative of the average adipose tissue secretion. In IL-6 infusion studies we have found that the metabolic clearance rate of IL-6 is ~1 l min^{-1} under resting conditions (Lyngsø *et al.* 2002). Thus, it is likely that the IL-6 secretion rate found in the anterior, abdominal, subcutaneous adipose tissue is higher than the secretion rates in other adipose tissue depots, although it has been shown in cell cultures that visceral adipose tissue produces ~3-fold more IL-6 than cells from subcutaneous adipose tissue (Fried *et al.* 1998). A higher IL-6 production rate in anterior, abdominal, subcutaneous adipose tissue compared with other adipose tissue regions would be in accord with our recent findings with respect to regional differences in the lipolytic rate (Enevoldsen *et al.* 2001). Second, the metabolic clearance rate of IL-6 may be smaller during exercise than during rest. However, this is hardly likely under the present experimental conditions. In a study performed in rats most IL-6 was found to be cleared in the liver (Castell *et al.* 1988). During exercise the splanchnic perfusion may decrease by ~50 %, but simultaneously the arterial IL-6 concentration increases ~2-fold, thus the IL-6 supply to the liver seems to remain more or less constant during exercise compared with rest. On the other hand, it is interesting to note that an IL-6 production rate of 6–7 ng min^{-1} after 1.5 h two-legged knee extensor exercise gave rise to an arterial IL-6 concentration close to that found in the present study (Steensberg *et al.* 2001). The difference between the arterial concentrations in the two studies by Steensberg *et al.* may be due to the metabolic clearance of IL-6 being lower after 4 h of one-legged knee extensor exercise than after 1.5 h of two-legged knee extensor exercise.

The increase in the circulating IL-6 concentration during exercise most likely stems from skeletal muscle (Papanicolaou *et al.* 1996; Orban *et al.* 1999; Steensberg *et al.* 2000; Pedersen *et al.* 2001). During exercise it was not possible to show a significantly increased IL-6 output from adipose tissue. Thus, adipose tissue does not seem to contribute to the higher arterial IL-6 concentration found during moderate exercise of short duration. The mechanisms eliciting the IL-6 production in skeletal

muscle and adipose tissue seem to be different. While the IL-6 production in skeletal muscle is stimulated by contraction and is related to the muscle glycogen content (Steensberg *et al.* 2001), the adipose tissue IL-6 production is not directly related to an increased lipolytic activity in the tissue *per se*. Sympatico-adrenergic mechanisms have been suggested to regulate the IL-6 production from adipose tissue (Mohamed-Ali *et al.* 2001) and also tumour necrosis factor α (TNFα) may induce IL-6 production (Akira *et al.* 1993). Therefore, the increased sympathetic activity during exercise immediately giving rise to a high lipolytic rate may also be the stimulus increasing the IL-6 output post-exercise either directly or indirectly via TNFα, since TNFα is stimulated by sympathetic mechanisms in adipose tissue (Orban *et al.* 1999). Recently it has been shown that 60–90 min of knee extensor exercise induces a transient increase in gene transcriptions of various metabolic genes in human skeletal muscle with a peak ~60 min post-exercise (Pilegaard *et al.* 2000), and a similar time frame has been found in adipose tissue *in vitro* with respect to various cytokine gene transcription rates (Bruun *et al.* 2001). It is tempting to speculate whether exercise induces gene transcription in adipose tissue with a similar time course based on the pattern of the IL-6 output from adipose tissue found in the present study. In another recent study (Keller *et al.* 2001) a transcriptional activation of the IL-6 gene has been demonstrated in contracting skeletal muscle, and it was suggested that this production during exercise may be an endocrine signal to the liver to enhance hepatic glucose production. In line with this hypothesis it could be suggested that the post-exercise adipose tissue IL-6 production may play a role in the co-ordination of the hepatic and adipose tissue lipid metabolism. As we have previously shown, a substantial fraction of the fatty acids mobilized from adipose tissue post-exercise is taken up in the liver (Bülow *et al.* 2000) , while only a modest amount is taken up in the previously exercising muscles in this period (Mulla *et al.* 2000).

In conclusion these experiments show that a moderate exercise bout of 60 min duration induces an increased IL-6 output from subcutaneous, abdominal adipose tissue for a prolonged period post-exercise. The physiological effect of this increase is not evident from the present experiments. However, it is hypothesized that the enhanced IL-6 production may act via autocrine/paracrine mechanisms promoting/modifying the post-exercise stimulation of lipolysis and fatty acid mobilization from this adipose tissue depot.

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Acknowledgements

This study was supported by grants from The Novo Nordic Foundation, The John and Birthe Meyer Foundation, and The Danish Heart Foundation (97-1-3-48-22465).